

### **REMARKS**

In the amendments above, Claims 2, 3, 7, 8, 10, 11, 20, 21, and 23-25 have been cancelled, Claims 1, 6, 9, 12-19, 22 and 26-29 have been amended, and new Claims 30 and 31 have been added, to more particularly point out and distinctly claim Applicants' invention. Claim 6 has been amended to correct a typographical error. A basis for the amendment may be found in page 4, line 19, of the specification as filed. Support for the amendments to Claim 9 may be found on page 4, lines 20-24, of the specification as filed. Support for new Claims 30 and 31 may be found on page 8, lines 22-25, of the specification as filed.

### **EXAMINER'S REJECTIONS**

In the Office Action dated June 14, 2007, the Examiner rejected Claim 27 under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by a credible asserted utility or a well established utility. Specifically, the Examiner maintained that Claim 27 is directed to a method of preventing bacterial or protozoan infection. The Examiner stated that the broadest reasonable interpretation of the term infection merely requires that one microorganism gain entry into the cells of a host. The Examiner maintained that there is no evidence that entry would be prevented, therefore that utility would not be credible.

The Examiner also rejected Claim 27 under 35 U.S.C. § 112, first paragraph. Specifically, the Examiner maintained that the claimed invention is not supported by either a credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention.

The Examiner rejected Claims 4, 5, 9, 13-15 and 19 under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regards as the invention.

The Examiner noted that Claim 1 reads on a 10% aqueous solution. The Examiner maintains that dependent Claim 4 reads on said solution further comprising up to 8% by weight of water and that dependent Claim 5 reads on said solution further comprising up to 6% by weight of water.

The Examiner maintained that it is not clear what is meant by the terminology, "citric acid is 1:1 a pH of 5" (Claim 9).

The Examiner maintained that the terminology "further comprising" renders Claims 13-15 and 19 indefinite as no additional process steps have been set forth.

The Examiner further rejected Claims 1, 4-6, 9, 12-17, 22, and 26-28 under 35 U.S.C. § 102(b) as being anticipated by Asero et al., U.S. Patent No. 6,277,829, ("Asero") or Khamar et al., PCT Published Patent Application No. WO 02/07736 ("Khamar"). The Examiner maintains that Asero discloses the claimed formulation comprising azithromycin and citric acid wherein the molar ratio of azithromycin to citric acid is about 1:0.67 to 1:1.5 and the pH is adjusted to 5.5-7.6 (column 6, lines 51-57) and having a concentration of 10% (column 4, lines 1-2); that Khamar discloses dissolving citric acid in water, adjusting the pH to 4 to 6 and adding azithromycin (page 4, Example 1); and that an addition salt comprising azithromycin and citric acid would have been inherently formed from such a process.

The Examiner rejected Claims 1, 4-6, 9, 12-19, 22 and 26-29 under 35 U.S.C. § 103(a) as being unpatentable over Asero or Khamar. The Examiner maintains that each of Asero and Khamar discloses combining citric acid and azithromycin but does not disclose isolation of azithromycin hydrogen citrate by crystallization and that, since crystalline azithromycin is well known in the art, such as azithromycin dehydrate disclosed by Khamar, a person having ordinary skill in the art at the time the claimed invention was made would have been motivated to crystallize citric salt of azithromycin

because said salt would have been expected to possess similar properties as known crystalline forms of azithromycin.

**35 U.S.C. § 101 and 35 U.S.C. § 112 Rejections**

Claim 27 is directed to a method of preventing bacterial or protozoan infection. The Examiner has found that the broadest reasonable interpretation of the term infection merely requires that the micro-organism gain entry into the cells of a host and there is no evidence that entry could be prevented. Therefore, that utility would not be credible and as a consequence one skilled in the art would not know how to use the claimed invention.

Applicants respectfully disagree with the Examiner's conclusion. Azithromycin is a broad-spectrum antibacterial agent commercialized by Pfizer in the United States as ZITHROMAX<sup>®</sup> (azithromycin capsules, tablets and oral suspension). The FDA approved label for ZITHROMAX<sup>®</sup> (NDA no. 050693) shows the following indications for azithromycin:

ZITHROMAX<sup>®</sup> (azithromycin) is indicated for the treatment of patients with mild to moderate infections (pneumonia: see WARNINGS) caused by susceptible strains of the designated microorganisms in the specific conditions listed below.

Applicants further note that the use of azithromycin as a preventive treatment is well known in the art. For example, azithromycin is known as a preventive treatment for *Mycobacterium avium* complex (MAC) and has been tested extensively in AIDS patients as the ZITHROMAX<sup>®</sup> label indicates:

To reduce the development of drug-resistance bacteria and maintain the effectiveness of Zithromax (azithromycin) and other antibacterial drugs, Zithromax (azithromycin) should be used only to treat or **prevent** infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting and modifying antibacterial therapy. In

the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy (emphasis added).

Prophylaxis of Disseminated *Mycobacterium avium* complex (MAC) Disease. ZITHROMAX<sup>®</sup>, taken alone or in combination with rifabutin at its approved dose, is indicated for the **prevention** of disseminated *Mycobacterium avium* complex (MAC) disease in person with advanced HIV infection (See DOSAGE and ADMINISTRATION, CLINICAL STUDIES) (Emphasis added).

The use of azithromycin for preventing bacterial or protozoan infection is well known in the art, and, as a consequence, one skilled in the art would know how to use the claimed invention. Accordingly, Applicants respectfully request that the Examiner withdraw the rejections to Claim 27 under 35 U.S.C. § 101 and under 35 U.S.C. § 112, first paragraph.

The Examiner has found that dependent Claims 4 and 5 are indefinite as both are dependent on Claim 1, which refers to a 10% aqueous solution.

In response, Applicants note that Claims 4 and 5 are directed to the content in water when the hydrogen citrate salt of azithromycin is in solid state. To better clarify the distinction, Claims 4 and 5 have been deleted and new Claims 30 and 31 have been added.

Additionally, the Examiner has found that the terminology “citric acid is 1:1 a pH of 5” on Claim 9 is not clear, and that the terminology “further comprising” renders Claims 13-15 and 19 indefinite .

In response, Applicants have amended Claim 9 by replacing the terminology “citric acid is 1:1 a pH of 5” with "citric acid is close to the stoichiometric ratio and has a pH of 5 in a 10% aqueous solution ...." Claims 13-15 and 19 have been amended by replacing the terminology “further comprising” with “wherein.”

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejections under 35 U.S.C. 112, second paragraph.

**35 U.S.C. § 102(a) Rejections**

Claim 1 has been rejected under 35 U.S.C. § 102(b) as being anticipated by Asero. Applicants note that Asero discloses a process for the preparation of an aqueous ophthalmic formulation containing azithromycin that comprises dissolving in an aqueous medium, an ophthalmically acceptable polybasic phosphate in an amount ranging from 7.8 to 68.6 g/l and citric acid monohydrate in an amount ranging from 0.9 to 35.94 g/l and azithromycin in an amount ranging from 0.1 to 100 g/l, wherein the molar ratio of azithromycin to citric acid ranges from 1:0.67 to 1:1.5.

Applicants note that anticipation requires that each and every element of the claims be disclosed, either expressly or inherently, in a single prior art reference or embodied in a single prior art device or practice. In the specification of the subject invention, the process allows one to obtain an extremely high solubility azithromycin in aqueous solution. However, Example 1 of Asero states that "[a]zithromycin has been added only when buffer agents are completely dissolved ...." Example 1 does not provide any information about the formation of an azithromycin salt. In fact, Asero states in the specification that polybasic phosphate/citric acid monohydrate mixture is used as buffer solution, thus teaching away from the synthesis of azithromycin salts in the presence of organic solvents (column 5, lines 29-37):

The process of the present invention is able to overcome any difficulties in preparing aqueous compositions containing azithromycin. In fact, it has been discovered a process in which, without being necessary to synthesize azithromycin salts in presence of organic solvents, it is possible, by adding appropriate amounts of citric acid/phosphate buffer ratio to the azithromycin suspension, to obtain a stable aqueous pharmaceutical form which is compatible to the ocular structures.

The Examiner maintains that an addition salt comprising azithromycin would have been inherently formed. However, according to the conditions described in the claims and the specification of Asero (azithromycin has two nitrogen groups of basic nature; citric acid has three COOH groups and has previously been mixed with dibasic disodium hydrogen phosphate), the ophthalmic formulation formed should comprise a mixture of azithromycin phosphate, citrate and sodium/citrate salts. Thus, under such conditions, azithromycin hydrogen citrate should not be formed, even in low percentage. Therefore, as Asero does not teach this element of Claim 1, the claims of the subject application are not anticipated by Asero.

Applicants again note that Claims 4 and 5 have been deleted and now correspond to new Claims 30 and 31, which are dependent upon Claims 28 and 29. As the rest of Claims 6, 9, 12-17, 22 and 26-28 and new Claims 30 and 31 are directly or indirectly dependent upon Claim 1, Applicants maintain that they are not anticipated by Asero.

Claim 1 has been rejected under 35 U.S.C. § 102(b) as being anticipated by Khamar. Applicants again note that anticipation requires that each and every element of the claims be disclosed, either expressly or inherently, in a single prior art reference or embodied in a single prior art device or practice. Khamar discloses a process of manufacturing a clear liquid pharmaceutical composition of azithromycin that comprises the steps of (a) adding azithromycin to a solvent with the appropriate pH and (b) mixing of the above preparation to obtain clear liquid preparation.

Example 1 of Khamar describes the production of the claimed composition which comprises a mixture of citric acid and azithromycin. Applicants note that the process according to Example 1 of Khamar teaches:

1. Citric acid anhydrous is dissolved in 200 ml Water for injection.
2. The pH of the above solution is adjusted to 4.0 to 6.0 with sodium hydroxide.

3. Azithromycin is added to this solution and mixed.
4. Now Sodium hydroxide solution is added until clear solution is added, and the pH is between 6.0 and 7.0.
5. The solution is filtered through 0.22 micron membrane and filled in vials.
6. The vials are then sterilized by autoclaving at 120°C with 15 LB pressure for 20 minutes.

Khamar does not disclose the isolation of the salt formed according to the process disclosed above. Although the Examiner stated that an addition salt comprising azithromycin could have been inherently formed from such a process, it is improbable that in such conditions azithromycin hydrogen citrate salt could be formed, even in low percentage.

According to the conditions disclosed by Khamar, citric acid is dissolved in water and the pH of the solution is adjusted from 4.0 to 6.0 with sodium hydroxide. In such conditions, monosodic salt of citric acid is formed. Azithromycin is then added to the solution, which reacts with the previously formed monosodic salt of citric acid to form a sodium azithromycin citrate salt instead of an azithromycin hydrogen citrate as taught by the subject invention. As the conditions according to Khamar would not result in the formation of azithromycin hydrogen citrate, Claim 1 is not anticipated by the Khamar reference.

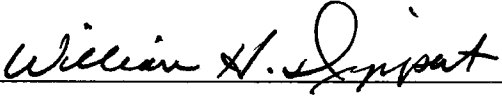
Claims 6, 9, 12-17, 22 and 26-28 and new Claims 30 and 31 depend directly or indirectly from Claim 1 and are not anticipated by Khamar's patent application. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 102(b).

In view of the comments above and the amendments to the claims, it should be clearly appreciated that the claims herein are patentable over Khamar and Asero. Accordingly, withdrawal of the rejections and allowance of the claims is believed proper.

Reconsideration and allowance of all the claims herein are respectfully requested.

Respectfully submitted,

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A handwritten signature in cursive script, reading "William H. Dippert", is written over a horizontal line.

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